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| APPLICATION NO.   | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO.          | CONFIRMATION NO. |
|---|-------------|----------------------|------------------------------|------------------|
| 10/574,194  | 03/02/2007  | Fumihiko Urano       | 07917-259US1<br>(UMMC04-35 a | 9270             |
| 26161   | 7590        | 01/02/2009           | EXAMINER                     |                  |
| FISH & RICHARDSON PC<br>P.O. BOX 1022<br>MINNEAPOLIS, MN 55440-1022 |             |                      | SZPERKA, MICHAEL EDWARD      |                  |
|   |             |                      | ART UNIT                     | PAPER NUMBER     |
|   |             |                      | 1644                         |                  |
|   |             |                      | NOTIFICATION DATE            | DELIVERY MODE    |
|   |             |                      | 01/02/2009                   | ELECTRONIC       |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

|                              |                                      |  |  |
|------------------------------|--------------------------------------|--|--|
| <b>Office Action Summary</b> | <b>Application No.</b><br>10/574,194 | <b>Applicant(s)</b><br>URANO, FUMIHIKO |  |
|                              | <b>Examiner</b><br>Michael Szperka   | <b>Art Unit</b><br>1644                |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 22 October 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-7, 13-27, 30-34, 47 and 48 is/are pending in the application.
- 4a) Of the above claim(s) 1-7, 13-23, 31, 47 and 48 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 24-27, 30 and 32-34 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/26/06</u> .  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

1. Applicant's response received October 22, 2008 is acknowledged.

Claims 8-12, 28, 29, and 35-46 have been canceled.

Claims 1-7, 13-27, 30-34, 47, and 48 are pending in the instant application.

Applicant's election of Group III, claims 24-27, 30, and 32-34, drawn to methods of screening to identify compounds that alter IRE1 activity, in the reply filed on October 22, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-7, 13-23, 31, 47, and 48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 22, 2008 as explained above.

Claims 24-27, 30, and 32-34 are under examination in this office action.

### ***Information Disclosure Statement***

2. The IDS received 12/26/06 is acknowledged and has been considered.

### ***Specification***

3. The title and abstract are objected to because they do not specify the instant claimed subject matter. Specifically, neither the title nor the abstract indicate screening methods to identify compounds that modulate IRE1 activity. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, claim 33 recites "contacting...with the agent... identified by the method of claim 33". Claim 33 is a method of identifying an agent, and thus the metes and bounds of the claim are unclear since it recites circular logic. Given that many claims, including claim 33 itself, depend from independent claim 24, it is unclear what limitations applicant is intending to incorporate by the reference to claim 33 within claim 33 itself. It is suggested that applicant amend the claim to recite the use of an agent identified in a different claim or amend the claim to remove the reference to limitations disclosed in a different claim.

6. Note that as discussed above, the limitations of claim 33 are unclear because the claim refers to itself. As such, the agent used in the contacting step is presumed, for the purposes of examination under art, to be the "test compound" of claim 24. Note that claim 33 depends from 24, and thus such an interpretation of claim 33 is plausible and reasonable.

### ***Claim Rejections - 35 USC § 102***

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section

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351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 24-27, 33, and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Bertolotti et al. (Nature Cell Biology, 2000, 2:326-332).

Bertolotti et al. disclose a model system in which they study ER stress by examining the interactions between IRE1 and ER chaperone proteins such as BiP (see entire document, particularly the abstract). During times of ER stress, misfolded proteins accumulate in the ER. The presence of misfolded proteins causes BiP to dissociate from IRE1, with BiP and other chaperones being responsible for helping proteins to fold properly and thus reduce the ER stress. Bertolotti et al. used a cell based model system wherein the phosphorylation state of IRE1 was detected by immunoblot (phosphorylated IRE1 has a greater apparent molecular mass due to the presence of highly charged phosphate group) in the presence and absence of thapsigargin and DTT, two agents known to increase ER stress because they cause proteins to misfold (see particularly the left column of page 328 and Figure 5). They also examined this model in the presence and absence of the "test compound" of overexpressed BiP, and observed that in the presence of excess BiP, IRE1 phosphorylation was decreased and ER stress was decreased since fewer misfolded proteins could accumulate due to the high level of chaperone proteins. Other "test proteins" investigated by Bertolotti et al. include mutant IRE1 polypeptides that could dimerize with wild type IRE1 yet were unable to be phosphorylated (see particularly Figures 3,6, 7, and page 329). Note that since excess BiP decreased the concentration of misfolded proteins, and thus ER stress, Bertolotti et al. identified BiP as a therapeutic agent to treat ER stress disorders.

Therefore, the prior art anticipates the claimed invention.

9. Claims 24-27, 30, 33 and 34 are rejected under 35 U.S.C. 102(e) as being anticipated by Ron et al. (US 2003/0224428 A1, of record).

Ron et al. disclose screening methods to identify agents that alter the phosphorylation of IRE1 using antibodies that bind to the phosphorylated form of IRE1 (see entire document, particularly the abstract, paragraphs 22-26, 38, and claims 1-3 and 14-17). Ron et al. also disclose that agents such as tunicamycin, thapsigargin, and DTT are used to increase ER stress in their model systems (paragraphs 15, 60, 64, 67-83).

Therefore, the prior art anticipates the claimed invention.

### ***Claim Rejections - 35 USC § 103***

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ron et al. (US 2003/0224428 A1, of record) in view of Kaufman et al. (US 2005/0250182 A1).

The disclosure of Ron et al. has been discussed supra and differs from the instant claimed method in that while the methods of Ron et al. are capable of discriminating between agents which do and do not increase IRE1 activity, Ron et al. do not explicitly state that agents which increase IRE1 activity (such as by increasing IRE1 phosphorylation) are useful as therapeutic agents.

Kaufman et al. disclose that activated IRE1 is phosphorylated and that IRE1 is responsible for activating XBP1, a transcriptional activator of the unfolded protein/ER stress response. Therefore, molecules which increase XBP1 activation are to be used to treat protein conformational diseases, particularly those that induce IRE1 to splice an mRNA molecule that encodes XBP1, thereby activating the unfolded protein response (see entire document, particularly paragraphs 2-5, 13-16 and 20, and most particularly paragraph 22).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the instant invention was made to identify agents that increase IRE1 activity using the assay disclosed by Ron et al. This is because activated IRE1 initiates the unfolded protein /ER stress response, and Kaufman et al. disclose that agents which accomplish this are to be used in methods of treating subjects with protein conformational diseases and disorders. Therefore, the ordinary artisan would want to identify agents that increase IRE1 activity such that they could be used to treat patients with protein conformational diseases and disorders.

12. No claims are allowable.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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